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(56) Documents Cited

GB 2182934 A

The Merck Manual, 1992, Merck Research
Laboratories, pp 1582 to 1587 and 1592 to 1599

(58) Field of Search

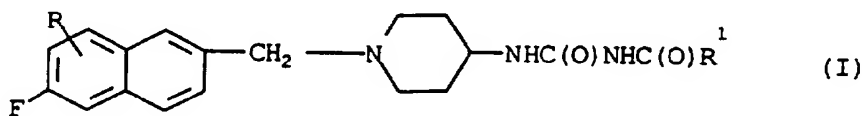
UK CL (Edition O) A5B BHA BJA BJB

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ONLINE: CAS ONLINE, WPI, JAPIO, CLAIMS,
DIALOG/MEDICINE

(54) Piperidine derivatives as 5-HT_{2C} receptor antagonists

(57) Piperidine derivatives of general formula I



wherein R¹ is 3- or 4-pyridyl and R is hydrogen or fluorine, and R is bonded to any of the vacant naphthalene ring positions, e.g. 5- or 7-,

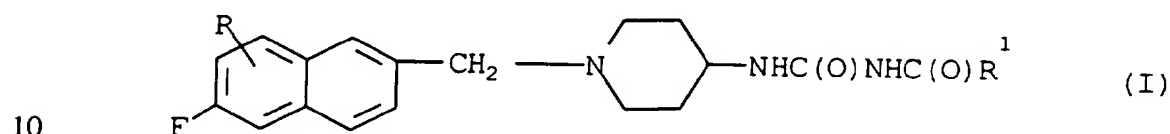
or pharmaceutically acceptable acid addition salts thereof, are useful in the treatment of anxiety, OCD or panic attacks and as 5-HT_{2C} receptor antagonists.

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MEDICAL TREATMENT

This invention relates to the use of certain piperidine
5 derivatives in the treatment of anxiety, OCD and panic
attacks.

The piperidine derivatives are those of general formula



or salts thereof, wherein R^1 is 3- or 4-pyridyl, R is
hydrogen or fluorine, and is bonded to any of the vacant
naphthalene ring positions, e.g. 5- or 7-.

15 The piperidine derivatives of formula (I) and their method
of preparation are disclosed in European Patent Publication
No 228795 (John Wyeth & Brother Limited). The compounds
have now surprisingly been found to inhibit the function of
20 the 5-HT_{2C} receptor.

The preferred compounds of formula (I) are:
N-[[[1-[(6-fluoro-2-naphthalenyl)methyl]-4-
piperidinyl]amino]carbonyl]-3-pyridinecarboxamide or N-
25 [[[1-[(6-fluoro-2-naphthalenyl)methyl]-4-piperidinyl]-
amino]carbonyl]-4-pyridine carboxamide
and their pharmaceutically acceptable acid addition salts.

The present provides in one aspect, a method of treating
30 anxiety, obsessive compulsive disorder (OCD) or panic
attacks which comprises administering to a mammal in need
thereof an effective amount of a compound of formula (I) as
defined above or a pharmaceutically acceptable acid
addition salt thereof. In a second aspect the invention
35 provides the use of a compound of formula (I) as defined
above or a pharmaceutically acceptable acid addition salt

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thereof for the manufacture of a medicament for the treatment of anxiety, obsessive compulsive disorder (OCD) or panic attacks. Suitably, the mammal is a human. Suitably, the compound is administered repeatedly.

5

In this specification the terms "treatment" and "treating" relate to the administration of the compounds to prevent the disorder as well as to treat the disorder or to alleviate the symptoms of the disorder.

10

The compounds may be used in their free base form or as acid addition salts.

Examples of acid addition salts are those formed from inorganic and organic acids, such as sulphuric, hydrochloric, hydrobromic, phosphoric, tartaric, fumaric, maleic, citric, acetic, formic, methanesulphonic, p-toluenesulphonic, oxalic and succinic acids.

20 The compounds may be used for treating anxiety, OCD or panic attacks in the form of pharmaceutical compositions which comprise a compound of formula I or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutically acceptable carrier.

25 Any suitable carrier known in the art can be used to prepare the pharmaceutical composition. In such a composition, the carrier is generally a solid or liquid or a mixture of a solid or liquid.

30 Solid form compositions include powders, granules, tablets, capsules (e.g. hard and soft gelatine capsules), suppositories and pessaries. A solid carrier can be, for example, one or more substances which may also act as flavouring agents, lubricants, solubilisers, suspending agents, fillers, glidants, compression aides, binders or
35 tablet-disintegrating agents; it can also be an encapsulating material. In powders the carrier is a finely divided solid which is in admixture with the finely divided

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active ingredient. In tablets the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99%, eg from 0.03 to 99%, preferably 1 to 80% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

The term "composition" is intended to include the formulation of an active ingredient with encapsulating material as carrier to give a capsule in which the active ingredient (with or without other carriers) is surrounded by the carrier, which is thus in association with it. Similarly cachets are included.

Liquid form compositions include, for example, solutions, suspensions, emulsions, syrups, elixirs and pressurised compositions. The active ingredient, for example, can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid carrier can contain other suitable pharmaceutical additives such as solubilisers, emulsifiers, buffers, preservatives, sweeteners, flavouring agents, suspending agents, thickening agents, colours, viscosity regulators, stabilisers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (particularly containing additives as above, eg cellulose derivatives, preferably sodium carboxymethyl cellulose solution), alcohols, eg glycerol and glycols) and their derivatives, and oils (eg fractionated coconut oil and arachis oil). For parenteral administration the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in

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sterile liquid form compositions for parenteral administration.

5 Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. When the compound is orally active it can be administered orally either in liquid or solid composition form.

10 Preferably the pharmaceutical composition is in unit dosage form, eg as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit

15 dosage forms can be packaged composition, for example packeted powders, vials, ampoules, prefilled syringes or sachets containing liquid. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package

20 form.

25 The quantity of the active ingredient in unit dose of composition may be varied or adjusted from 0.5 mg or less to 750 mg or more, according to the particular need and the activity of the active ingredient.

The following Examples illustrate the invention:

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Example 1

5

Preparation of Tablets

		<u>Amount per tablet mg</u>		
10				
	N-[[[1-[(6-fluoro-2-naphthalenyl)			
	methyl]-4-piperidinyl]amino]			
	carbonyl]-3-pyridinecarboxamide	1	5	10
15				
	Microcrystalline cellulose	49.25	47.25	44.75
	Modified food corn starch	49.25	47.25	44.75
20	Magnesium stearate	0.5	0.5	0.5

Tablets are prepared from bulk amounts of ingredients in the proportions given above.

25

All of the active compound, cellulose and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the

30 magnesium stearate. The resulting granulation is then compressed into tablets containing 1, 5 and 10 mg of the active ingredient per tablet.

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5

Example 2Preparation of powder filled capsules

10

Amount mg

N-[[[1-[(6-fluoro-2-naphthalenyl)
methyl]-4-piperidinyl]amino]

15 carbonyl-4-pyridine carboxamide

10

15

Avicel

45

20 Lactose

153

Starch (1500 NF)

-

117

Sodium starch glycollate

-

6

25

Magnesium stearate

2

2

30

The formulations are prepared by admixing the ingredients in the proportions given above and filling two-part hard gelatin capsules with the required amount of the resulting mixture to give capsules containing 10 or 15 mg of the active compound.

35

Example 3

5

N-[[[1-[(6-Fluoro-2-naphthalenyl)methyl]-4-piperidinyl]amino]carbonyl-3-pyridine carboxamide, dihydrochloride, hemihydrate (WY 27587) (10 mg/kg p.o. 10 b.i.d.) or vehicle was administered to rats for 14 days and behavioural testing performed 24 hours after the last dose. The hypolocomotor response (cf Knight and Fletcher, 1989, *Br J Pharmacol.*, 97, 461P) to 6-chloro-2-(1-piperazinyl)pyrazine hydrochloride) (MK-212) (0.75 and 2.0 15 mg/kg i.p. 30 min predose; n=6) was measured for a 2 min period using automated open fields. Results are set out in Table 1.

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Table 1: Effects of Wy 27587 on MK-212-induced hypolocomotion

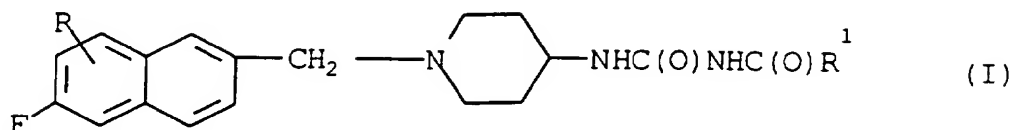
5	MK-212 (mg/kg i.p.)	Locomotor activity	
		<u>mean \pm standard error mean</u>	
		<u>Vehicle</u>	<u>WY 27587</u>
10			
	0	120.5 \pm 5.3	127.8 \pm 7.1
	0.75	92.3 \pm 7.3*	110.7 \pm 2.9*
	2	28.3 \pm 7.1**	66.8 \pm 4.1**\$

15 *P<0.05; **P<0.001 versus respective vehicle-controls;
 \$P<0.05 versus respective chronic-vehicle group using two-way ANOVA/Fisher's protected LSD (locomotor activity).

CLAIMS:

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1. A piperidine derivative of general formula I



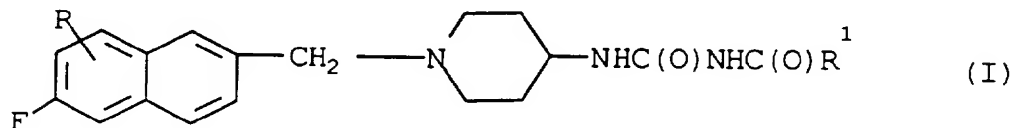
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wherein R^1 is 3- or 4-pyridyl and R is hydrogen or fluorine, and R is bonded to any of the vacant naphthalene ring positions, e.g. 5- or 7-,

15

or a pharmaceutically acceptable acid addition salt thereof, for use as a 5-HT_{2C} receptor antagonist.

- 20 2. A piperidine derivative of general formula I



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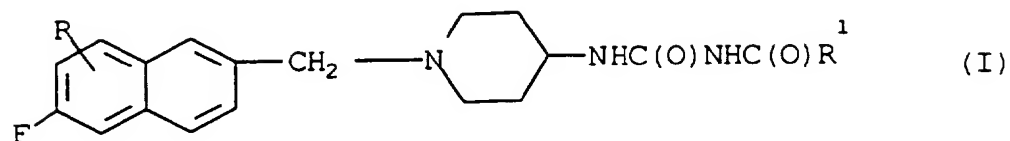
wherein R^1 is 3- or 4-pyridyl and R is hydrogen or fluorine, and R is bonded to any of the vacant naphthalene ring positions, e.g. 5- or 7-,

- 30 or a pharmaceutically acceptable acid addition salt thereof, for use in the treatment of anxiety, OCD or panic attacks.

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3. The use of a piperidine derivative of general formula I

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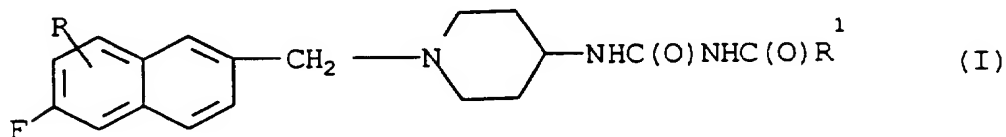


wherein R^1 is 3- or 4-pyridyl and R is hydrogen or
10 fluorine, and R is bonded to any of the vacant naphthalene
ring positions, e.g. 5- or 7-,

or a pharmaceutically acceptable acid addition salt
thereof, in the manufacture of a medicament for use as a 5-
15 HT2C receptor antagonist.

4. The use of a piperidine derivative of general formula I

20



wherein R^1 is 3- or 4-pyridyl and R is hydrogen or
25 fluorine, and R is bonded to any of the vacant naphthalene
ring positions, e.g. 5- or 7-,

or a pharmaceutically acceptable acid addition salt
thereof, in the manufacture of a medicament for the
30 treatment of anxiety, OCD or panic attacks.

5. A use as claimed in claim 3 or claim 4 wherein the
compound of formula I is:

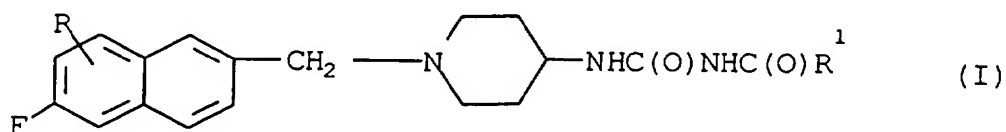
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N-[[[1-[(6-fluoro-2-naphthalenyl)methyl]-4-piperidinyl]amino]carbonyl]-3-pyridinecarboxamide; or
 N-[[[1-[(6-fluoro-2-naphthalenyl)methyl]-4-piperidinyl]-amino]carbonyl]-4-pyridine carboxamide

5 or a pharmaceutically acceptable acid addition salt of one of these compounds.

6. A pharmaceutical composition comprising a piperidine derivative of general formula I

10



15 wherein R¹ is 3- or 4-pyridyl and R is hydrogen or fluorine, and R is bonded to any of the vacant naphthalene ring positions, e.g. 5- or 7-,

or a pharmaceutically acceptable acid addition salt
 20 thereof, and a pharmaceutically acceptable diluent or carrier for use in the treatment of anxiety, OCD or panic attacks.



The
Patent
Office

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Application No: GB 9608631.9
Claims searched: 1 to 6

Examiner: Mr S.J.Pilling
Date of search: 12 August 1996

Patents Act 1977 Search Report under Section 17

Databases searched:

UK Patent Office collections, including GB, EP, WO & US patent specifications, in:

UK Cl (Ed.O): A5B (BHA, BJA, BJB)

Int Cl (Ed.6): A61K 31/445

Other: ONLINE: CAS ONLINE, WPI, JAPIO, CLAIMS, DIALOG/MEDICINE

Documents considered to be relevant:

Category	Identity of document and relevant passage	Relevant to claims
X:Y	GB 2182934 A (JOHN WYETH & BROTHER) see page 1 lines 49 to 60, page 2 lines 60 to 61 and page 4 line 55 to page 5 line 30.	X:1,2,6 Y:4,5
Y	"The Merck Manual", published 1992 (16th edition), Merck Research Laboratories, see pages 1582 to 1587 and 1592 to 1599	4,5

X	Document indicating lack of novelty or inventive step	A	Document indicating technological background and/or state of the art.
Y	Document indicating lack of inventive step if combined with one or more other documents of same category.	P	Document published on or after the declared priority date but before the filing date of this invention.
&	Member of the same patent family	E	Patent document published on or after, but with priority date earlier than, the filing date of this application.